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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Rajagopalan, et al.
Serial No.:	09/898,809
Filed:	July 3, 2001
Group Art Unit:	1624
Confirmation No:	5120
Examiner:	McKenzie
Title:	**DYE-SULFENATES FOR DUAL PHOTOTHERAPY**
Our Ref. No.:	MRD-63

Cincinnati, Ohio 45202

February 19, 2003

Assistant Commissioner for Patents
Washington, D.C. 20231

DECLARATION OF RAGHAVAN RAJAGOPALAN PURSUANT TO 37 C.F.R. §1.132

Sir:

I, RAGHAVAN RAJAGOPALAN, declare as follows:

1. I am a named inventor in the above-identified patent application.

2. I hold a Ph.D. in Organic Chemistry from Columbia University. I have 20 years of experience in the synthesis and use of compounds for medical diagnosis and

therapy, which is the subject of the application. I have read the outstanding Office Action, and Interview Summary of January 29, 2003, and understand the position of the Examiner.

3. Regarding the definition of cyanine dyes in claims 1, 2, 11-14, and 23-30, I respectfully disagree with the Examiner's position that there are competing differences in the art as to the meaning or identity of cyanine dyes. The diquinoline compound cited by the Examiner as a specific cyanine compound with a registry number falls within a broad definition of the term cyanine. It is the broad definition which is encompassed by this invention, as evidenced by the following analysis.

4. One skilled in the art knows that "cyanines" encompass any cationic dye in which two nuclei of different or the same nature are linked by a mono or polymethine chain. Various cyanine dyes, well known in the art, have been used as contrast agents for various medical applications. One of the most commonly known cyanine dyes is indocyanine green that has been used in organ blood flow measurements.

5. A textbook used in this art states that "According to general usage, the term "cyanine" designates any cationic dye in which two nuclei of different or same nature are linked by a mono or polymethine chain." H. Larive and R. Dennilauler, "Cyanine Dyes Derived from Thiazolium Salts" in Thiazole and its Derivatives, J.V. Metzger, Ed.; pp. 23-30; John Wiley & Sons, New York, 1979) (emphasis added) (copy attached).

6. A chemical dictionary defines "cyanine dyes" broadly: "One of a series of dyes consisting of two heterocyclic groups (usually quinoline nuclei) connected by a chain of conjugated double bonds containing an odd number of carbon atoms. Example: cyanine blue $C_2H_5NC_9H_6$:$CHC_9H_6NC_2H_5$. They include the isocyanines, merocyanines, cryptocyanines, and dicyanines." (emphasis added) (copy attached).

7. The chemistry of cyanines is similar; all cyanines have a conjugated azamethine polyene system which contains a cationic nitrogen atom at one end and a neutral, tertiary nitrogen at the other end. Thus, "cyanines" encompass any cationic dye that is composed of two nuclei, of a different or the same nature, that are linked by a mono or polymethine chain. One of the nuclei has a cationic nitrogen, and the other nuclei has a neutral, tertiary nitrogen. This enables the electron to shuttle between the two remote nitrogen atoms. Rings attached to the nitrogen do not contribute substantially to the electronic transition, however, the presence of aromatic rings confer stability.

8. The nomenclature of cyanines is similar; for example, when the methine groups in the conjugated azamethine polyene system are partially or totally replaced by a nitrogen atom, the cyanine dye is called an azacyanine. The quinoline heterocycle cited by the Examiner is only one example of the family of cyanine dyes, which include carbocyanine, indocyanine, phthalocyanines, etc. These are examples from the family of cyanine dyes.

9. For the above reasons, I respectfully assert that the cyanine dye is definite and fully enabled.

10. With respect to the structures encompassed by the epitope in the inventive compound, I respectfully disagree with the Examiner's position. In my opinion, one skilled in the art would recognize that E is selected, based upon the target site for the compound, from compounds which bind to the desired target. In my opinion, the application fully discloses the broad classes encompassed by E, enabling one skilled in the art to select the identity of E based upon the target site.

11. The epitope in the inventive dye-sulfenate compounds directs these compounds to a target cell. For targeting, E is a region of a molecule that specifically bind to the target site on a cell (page 12, lines 17-18). Examples include an antibody, a peptide, a peptidomimetic, a carbohydrate, a glycomimetic, a drug, a hormone, or a nucleic acid The target site may be a somatostatin receptor, a heat sensitive bacterioendotoxin receptor, a neurotensin receptor, a bombesin receptor, a cholecystekinin receptor, a steroid receptor, or a carbohydrate receptor. Theses are disclosed in the application, at least a page 8, lines 17-20; and page 10, lines 12-14.

12. Different target cells may require different types of epitopes incorporated into the structure of the photosensitive compound to direct the compound to the particular type of cell. For example, if the target site is a tumor with sensitivity to estrogen, such as a mammary tumor, one skilled in the art would select a compound

which binds to an estrogen receptor to target the compound to the tumor. Phototherapy would then occur. Estrogen is one compound that would target an estrogen receptor. However, a compound with a structure similar to estrogen may also target and bind to the estrogen receptor but likely with less affinity and avidity than estrogen. This may include other steroid hormones such as progesterone, estradiol, estrone, 2-hydroxy estrone, 16 α-hydroxyestrone, 2-methoxyestrone, and estriol.

13. An epitope (E) is a single recognition site on a particular region of a molecule that recognizes and binds to another site on another molecule. Such binding occurs in antibody-antigen interactions, hormone and drug-cell surface structures, enzyme-substrate complexes, etc. Epitopes can be composed of carbohydrates, lipids or amino acids. A large molecule can also display more than one epitope and each one may recognize a different site on another molecular structure. Thus, one skilled in the art would know that targeting may vary widely but would know the repertoire from which to select a likely targeting compound, E.

14. In further support of my opinion that one skilled in the art would be capable of selecting a structure to target a specific site without undue experimentation based upon the disclosure, I provide examples when E is an amino acid, peptide, or peptidomimetic. Based upon the chemical structure and known binding compounds for, for example, somatostatin, bombesin, and neurotensin receptors, one skilled in the art would select E based upon the respective structures of somatostatin (a peptide of 14 amino acids), bombesin (also a peptide of 14 amino acids), and neurotensin (a peptide

of 13 amino acids). One skilled in the art would appreciate that a peptide having homology to any of these may also be effective, and could obtain such a peptide without undue experimentation (for example, by automated peptide synthesis or by purchase from a commercial source).

15. In still further support of my opinion, one skilled in the art would know that when E is cholecystekinin (a polypeptide of 33 amino acids) or related compounds, the compound is targeted to cholecystekinin receptors. The disclosure states that when E is dihyroxyindolecarboxylic acid or other melanin-producing biosynthetic intermediates, skin tumors may be targeted; one skilled in the art would know the identity of melanin-producing biosynthetic intermediates. The disclosure states that vascular lesions, such as atherosclerotic plaques, may be targeted with the compound when E is an integrin; one skilled in the art would know that integrin is a family of compounds related to the fibroblast fibronectin receptor, and are all heterodimers with α chains and β chains homologous to those of the fibronectin receptor, whose sequence is known by one skilled in the art.

16. I respectfully disagree with the Examiner's assertions that the disclosure is not enabling because no procedure is given to determine the affinity of receptor binding, and that the predictability in the art of preparing antibodies is low. The claims are directed to the inventive dye-sulfenates and methods for performing a phototherapeutic procedure using the inventive dye-sulfenates, not to binding of the inventive compounds to a particular receptor with a particular affinity. Further,

preparation of antibodies, in my opinion, antibodies are by nature specific and thus highly predictable. This predictable specificity is one reason that preparation of an antibody is routinely performed in characterizing an antigen. The methods to prepare, screen, and select antibodies are also known to one skilled in the art.

17. In my opinion, the disclosure is fully enabling. For example, I state:

> For tumors, the biomolecule is selected from the class of tumor markers including, but not limited to, somatostatin, bombesin, neurotensin, cholecystekinin, heat sensitive bacterioendotoxin, estrogen, and progesterone receptor binding compound. For vascular lesions, the biomolecule may be selected from the class of integrins, selectins, vascular endothelial growth factor, fibrins, tissue plasminogen activator, thrombin, LDL, HDL, Sialyl Lewis^x and its mimics, and atherosclerotic plaque bonding compounds.

Page 15, line 23 to page 16, line 7.

18. For the above reasons, I respectfully assert that the structure of E is definite and fully enabled.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the subject application or any patent issued thereon.

February 19, 2003
Date

Raghavan Rajagopalan
Raghavan Rajagopalan, Ph.D.